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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BAUM, STUART F	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/602,840	KIRIHARA ET AL.	
	Examiner	Art Unit	
	Stuart F. Baum	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72,73,78,79,84,86,88-91 and 95-110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72,73,78,79,84,86,88-91 and 95-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Appeal Brief submitted on 5/26/2004 is acknowledged. Finality of the previous office action is withdrawn and a non-final office action is set forth.

2. Claims 72-73, 78-79, 84, 86, 88-91, and 95-110 are pending and examined in the present office action.

Specification

3. The first line of the specification should be amended to state that application number 08/763,704 is now U.S. Patent Number 6,326,527.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 72-73, 78-79, 84, 86, 88-91, and 95-110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection includes dependent claims.

The term "substantially" in claims 72-73, 88-91, 97-98, 102-107 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicants use the term in conjunction with "identical", i.e., substantially identical and "complementary", i.e., substantially complementary. Applicants have not defined the metes and

bounds of these phrases so that one of skill in the art would be able to ascertain exactly which nucleic acids are encompassed by Applicants claims.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 72-73, 78-79, 84, 86, 88-91, and 95-110 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is repeated for the reasons of record set forth in the Official action mailed 12/22/2003. Applicant's arguments filed with the Appeal Brief on 5/26/2004 have been fully considered but they are not persuasive.

The claims are drawn to a transgenic *Zea mays* plant having an increased starch content or an increased starch extractability comprising transforming a maize plant with a DNA sequence that is substantially identical or complementary to an mRNA molecule encoding a 19kD or 22kD α-zein seed storage protein in an amount sufficient to decrease the amount of said seed storage protein, or comprising a DNA sequence that is substantially complementary or substantially identical to all or a portion of an mRNA molecule encoding a 19kD or 22kD α-zein seed storage protein; a method of producing a *Zea mays* seed with an increased starch content or a method of obtaining starch from a *Zea mays* seed comprising transforming a maize plant with a DNA sequence that is substantially identical or complementary to an mRNA molecule encoding

a 19kD or 22kD α-zein seed storage protein, or comprising transforming a maize plant with a DNA molecule that is substantially identical or substantially complementary to all or a portion of the mRNA sequence encoding any seed storage protein or encoding a 19 or 22 kD α-zein protein; or a transgenic *Zea mays* plant having an increased starch content or an increased starch extractability or a method of producing a *Zea mays* seed with an increased starch content, both plant and method comprising transforming a maize plant with a DNA sequence that is substantially identical or complementary to an mRNA molecule encoding a 19kD or 22kD α-zein seed storage protein and further transforming the plant with a DNA sequence encoding a polypeptide that provides the transgenic maize plant with increased kernel hardness.

Applicants disclose cDNA clone A20 of SEQ ID NO:1 that encodes a 19 kD α zein and a cDNA clone Z4 SEQ ID NO:2 that encodes a 22 kD α zein of (page 53, lines19-21 and page 55, lines 24-25).

Applicants do not identify structural features unique to the maize 19 and 22 kD α-zein proteins that distinguish it from other storage proteins nor do they describe other nucleic acid molecules encoding seed storage proteins encompassed by the claims, nor do they describe a DNA sequence encoding a polypeptide that provides increased kernel hardness.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of

what the gene does, rather than what it is. The court goes on to say, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of polynucleotide sequences encoding a 19kD or 22kD α-zein seed storage protein falling within the scope of the claimed genus of polynucleotides which are substantially identical or substantially complementary to all or a portion of an mRNA encoding a 19kD or 22kD α-zein seed storage protein. In addition, Applicants fail to describe any nucleic acids encoding polypeptides that increase kernel hardness. Applicants only describe two cDNA sequences encoding a 19kD or 22kD α-zein seed storage protein. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of polynucleotides. Given the lack of description of the necessary elements essential for the 19kD or 22kD α-zein seed storage protein, it remains unclear what features identify a 19kD or 22kD α-zein seed storage protein and what features need to be present in nucleic acid molecules that are substantially identical or substantially complementary to all or a portion of a 19kD or 22kD α-zein seed storage protein. Since the genus of 19kD or 22kD α-zein seed storage protein has not been described in enough detail to allow one to identify nucleic acid molecules that are substantially identical or substantially complementary to all or a portion of a 19kD or 22kD α-zein seed storage protein, the specification fails to provide an adequate written

description to support the breath of the claims. Applicants fail to meet either prong of the test set forth in *Eli Lilly*.

Applicants contend that "substantially identical or complementary" define a discrete class of subject matter that is well more than adequately described. As described, such sequences must hybridize *in vivo* to 19 kD or 22 kD α-zein genes so as to yield a decrease of expression of said α-zeins (page 9, middle paragraph).

The Office contends that homology or sequence identity is not a structural feature of a nucleic acid molecule. All nucleic acid molecules are composed of the same four nucleotides. Applicants fail to point with specificity the structural features that are common among and unique to the claimed genus of nucleic acid molecules. The Office contends that Applicants have defined nucleic acids encoding 19 kD and 22 kD α-zeins to comprise nucleic acid molecules that are at least about 65% identical to Applicants SEQ ID NO:1 or 2 but, Applicants have not disclosed any nucleic acid sequences with at least about 65% identity to SEQ ID NO:1 or 2 that hybridize *in vivo* to 19 kD or 22 kD α-zein genes so as to yield a decrease of expression of the 19 kD or 22 kD α-zein genes. In fact, nucleic acids that are at least about 65% identical to Applicants' SEQ ID NO:1 or 2, are below the percent identity threshold for nucleic acids encoding α-zeins as taught by Marks et al (1985).

Applicants contend that structural features unique to maize 19 kD and 22 kD α-zein plant seed storage proteins have been fully described in the specification. Applicants contend that conserved functional domains that are shared among zeins are exhibited in Figure 1. Applicants contend that functional domains of 19 kD α-zeins are described on page 2, lines 19-24 (paragraph bridging pages 9 and 10).

The Office contends that Figure 1 and the specification (page 2, lines 20-24) disclose regions which are conserved among three zein subfamilies and do not present structural features that are common and unique to just the 19 kD or 22 kD α-zeins. Applicants have defined a claimed sequence as one that exhibits at least about 65% identity to SEQ ID NO:1 or 2 and when overexpressed will yield a decrease of expression of the 19 kD or 22 kD α-zein. Applicants have not presented information specific for the 19 kD or 22 kD α-zeins but rather for the three subfamilies of α-zeins.

Applicants contend that Marks et al (1985) teach common structural characteristics shared among 19 kD and 22 kD α-zeins. Applicants contend that Marks et al teach that the 19 kD and 22 kD group of α-zein sequences are 75% to 95% and 92% homologous, respectively (page 10, middle paragraph, of Appeal Brief filed 5/26/2004).

The Office contends that Applicants' definition of "substantially identical" and "substantially complemetary" in which these terms encompass nucleic acids that are at least about 65% identical to Applicants' SEQ ID NO:1 or 2, Applicants claims are drawn to nucleic acid molecules whose sequence identity is below that which is taught by Marks et al. Therefore, the claims are drawn to sequences that would not necessarily encode a 19 kD or 22 kD α-zein storage protein and then they could not be used as an antisense molecule to down regulate the respective zein proteins.

Enablement.

6. Claims 72-73, 78-79, 84, 86, 88-91, and 95-110 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such

a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection has been modified from the first action set forth 2/13/2002 to include additional supporting references. Applicants' arguments filed with the Appeal Brief 5/26/2004 have been fully considered but they are not persuasive.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are drawn to a transgenic *Zea mays* plant having an increased starch content or an increased starch extractability comprising transforming a maize plant with a DNA sequence that is substantially identical or complementary to an mRNA molecule encoding a 19kD or 22kD α-zein seed storage protein in an amount sufficient to decrease the amount of said seed storage protein, or comprising a DNA sequence that is substantially complementary or substantially identical to all or a portion of an mRNA molecule encoding a 19kD or 22kD α-zein seed storage protein; a method of producing a *Zea mays* seed with an increased starch content or a method of obtaining starch from a *Zea mays* seed comprising transforming a maize plant with a DNA sequence that is substantially identical or complementary to an mRNA molecule encoding a 19kD or 22kD α-zein seed storage protein, or comprising transforming a maize plant with a

DNA molecule that is substantially identical or substantially complementary to all or a portion of the mRNA sequence encoding any seed storage protein or encoding a 19 or 22 kD α-zein protein; or a transgenic *Zea mays* plant having an increased starch content or an increased starch extractability or a method of producing a *Zea mays* seed with an increased starch content, both plant and method comprising transforming a maize plant with a DNA sequence that is substantially identical or complementary to an mRNA molecule encoding a 19kD or 22kD α-zein seed storage protein and further transforming the plant with a DNA sequence encoding a polypeptide that provides the transgenic maize plant with increased kernel hardness.

Applicants disclose cDNA clone A20 of SEQ ID NO:1 that encodes a 19 kD α zein and a cDNA clone Z4 of SEQ ID NO:2 that encodes a 22 kD α zein (page 53, lines19-21 and page 55, lines 24-25). Applicants teach transformed maize plants with constructs comprising the Z4 and A20 cDNA clones operably linked to the Z10 promoter in antisense orientation (page 74, Example 5, first paragraph). The resultant kernels or seeds exhibited an increased amount of the amino acid lysine and a decreased amount of leucine (page 77, lines 6-11; see also page 78, Table V and page 83, Table VI).

Applicants do not teach transgenic maize plants transformed with other DNA's encoding other 19 kD or 22 kD α-zein proteins, or Applicants do not teach any maize plants with increased overall starch content, including non-seed tissue.

Furthermore, the state-of-the-art for manipulation of starch content in plants is highly unpredictable. Coleman et al (1997, PNAS 94:7094-7097) teach that efforts to improve protein quality of maize seeds have focused on increasing the lysine content of the protein bodies within the endosperm. Two "high-lysine" mutants were identified, opaque2 (o2) and floury2 (fl2)

which have a higher lysine content due to a reduction in the α-zein protein content of the endosperm. However, this reduction in α-zein protein content is concomitant with an inferior endosperm quality (page 7094, left column, 2nd paragraph). Therefore, based on Coleman et al, one of skill in the art would predict that reducing the α-zein protein content of maize seeds using the strategy of the Applicants, will not increase the starch content of maize seeds.

Similarly, antisense inhibition of gene expression in plants is highly unpredictable. For example, Bryant (1989, Trends in Biotechnology 7(2):20-21) teaches using antisense to downregulate chalcone synthase did not always produce plants with the desired result. It was not clear why plants were produced with all levels of regulated chalcone synthase, from plants exhibiting suppression to plants exhibiting a wild-type phenotype (page 20, right column, 1st paragraph). Bryant suggests that "position effect" influences transgene expression (page 20, right column, 2nd paragraph). Furthermore, antisense molecule need to be 100% identical to their target sequence for down-regulating the target protein. Emery et al (2003, Current Biology 13:1768-1774) disclose experiments in which a target sequence of a micro-RNA was changed by two base-pairs. The altered base-pairs caused the complementary micro-RNA not to bind to the target sequence, which subsequently led to an increased expression of the target sequence's encoded protein (page 1769, right column, 2nd full paragraph). Therefore, antisense molecules that are less than 100% identical to the target sequence are not expected to hybridize with said target sequence.

One skilled in the art would not expect to achieve an increased starch content in all tissues of the plant using a DNA encoding a seed storage protein. α-zeins are storage proteins specific to seeds. Transforming a plant with a sequence encoding a 19 kD or 22 kD α-zein seed

storage protein will not affect expression of said seed storage proteins in non-seed tissue because said proteins are not normally expressed in non-seed plant tissue.

Given the limited guidance in the instant specification, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified sequences, either by using non-disclosed fragments of SEQ ID NO:1 or 2 as probes or by designing primers to undisclosed regions of SEQ ID NO:1 or 2 and isolating or amplifying fragments, subcloning the fragments, producing expression vectors and transforming plants therewith, in order to identify those, if any, that when over-expressed increase the starch content of a maize plant or seed and would be considered to be substantially identical or substantially complementary to all or a portion of a 19 kD or 22 kD α-zein seed storage protein.

Therefore, given the breadth of the claims; the lack of guidance and examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue trial and error experimentation would be required to practice the claimed invention, and therefore the invention is not enabled.

Applicants contend that no basis has been provided to doubt the enablement of the claims. Applicants contend that the Coleman et al (1997) reference that the Examiner used to support the enablement rejection, in fact, demonstrates enablement of the invention. Applicants contend that Coleman et al teach high-lysine mutants exhibiting a reduction of α-zein content were "concomitant with an inferior endosperm quality". Applicants contend that the "inferior" endosperm is in fact a "soft and starchy endosperm", and therefore the reference shows the direct correlation between increased lysine, decreased α-zein and soft and starchy endosperm (page 11,

2nd and 3rd paragraphs). Applicants also contend that "an 'inferior' endosperm does not equate to an inability to increase starch content or extractability" (page 12, 2nd paragraph). Applicants further contend that endosperm cells in a maize kernel are made up primarily of large starch granules and protein sequestered in protein bodies. Decreasing the amount of seed storage protein will therefore increase the relative starch content of the kernel (page 14, middle paragraph).

The Office does not interpret "soft and starchy endosperm" to mean an increase in starch content. Normal endosperm in maize seeds contains starch. Coleman et al describe the *floury* mutant in which the normal consistency of the endosperm has been changed to a "soft and starchy endosperm". Coleman et al do not disclose that the normal amount of starch in a wild-type maize seed has been increased in the *floury* mutant seeds. The Office believes Applicants equate "a soft and starchy endosperm" as recited in Coleman et al with an increased amount of starch or an increased starch extractability. The Office contends that Applicants have not shown a nexus between decreasing the amount of 19 kD or 22 kD α-zein seed storage proteins in maize kernels with an increased amount of starch or an increased starch extractability. Given the lack of disclosure for an increased amount of starch in the *floury* mutant and given the lack of disclosure that Applicants' method also increases the amount of starch in a maize seed, the Office maintains that Applicants are not enabled for a method to increase starch content of maize seeds. Applicants are invited to submit a 1.132 declaration providing evidence of increased starch levels or increased starch extractability in transformed maize plants.

Applicants contend that Marks et al (1985) supports enablement of the claims. Marks et al states that the 22 kD α-zein polypeptides exhibit a 92% homology while the clones

corresponding to the 19 kD α-zein exhibit a homology between 75% to 95%. Applicants contend that Marks et al demonstrates the common structural characteristics shared among 19 kD and 22 kD α-zeins. Applicants contend that no basis has been provided by the Examiner to indicate that different isoforms have "divergent functions". Applicants also contend that there is no support in the Marks et al reference for the prior contention that any of the mRNA isoforms described encode proteins other than zeins (paragraph bridging pages 12 and 13, and page 13, 2nd paragraph).

The Office contends that Marks et al does support the assertion that the broadly claimed invention is not enabled. Applicants' claims are drawn to nucleic acid sequences that are "substantially identical" or "substantially complementary" to an mRNA encoding a 19 kD or 22 kD α-zein plant seed storage protein. Applicants define "substantially identical" or "substantially complementary" as nucleic acid or amino acid sequences having at least about 65% sequence identity or homology to a nucleic acid sequence encoding a 19 kD or 22 kD α-zein plant seed storage protein. Given that Marks et al indicate that cDNA sequences among the 19 kD α-zein group are 75% to 95% identical and cDNA sequences among the 22 kD α-zein group are 92% identical, Applicants' sequences that are 65% identical fall below the threshold indicated by Marks et al and as such must not encode an α-zein storage protein and therefore will not decrease the activity of endogenous 19 kD or 22 kD α-zein seed storage proteins when overexpressed in a maize plant.

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart F. Baum whose telephone number is 571-272-0792. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Stuart F. Baum Ph.D.
Patent Examiner
Art Unit 1638
August 3, 2004

ELIZABETH MCELWAIN
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